REMARKS

Applicants respectfully request reconsideration and reexamination of the present application in light of the amendments and the remarks below.

Claims 1, 3-5, and 12-15 are pending in this application. Claims 9-11 were cancelled in the Reply and Amendment submitted on December 21, 2005. Claims 2 and 6-8 have been cancelled as being drawn to non-elected subject matter.

Claims 1 and 3-5 have been amended, and new claims 12-15 have been added. Support for the amendments and new claims is found throughout the application as originally-filed and from the pending and original claims. Exemplary support for the amendments and new claim is as follows. Support is provided with respect to a particular paragraph(s) and/or line numbers of the corresponding published U.S. application, Pub. No. 2002/0106685.

Support for "selecting at least two molecular markers of cervical cancer" can be found, for example, at lines 1-6 of paragraph 19 and lines 1-2 of paragraph 39.

Support for "combining the color signal intensities" can be found, for example, at paragraph 42.

Support for "measuring and accrediting the combined color signal intensities" can be found, for example, at paragraph 42.

Support for three molecular markers of claim 5 can be found, for example, at paragraph 37.

Support for a "diagnostic expert system" can be found, for example, at paragraph 24.

Support for "simultaneously detecting color signal intensities from said markers at a first wavelength" and "repeating said detection at a second wavelength" can be found, for example, at paragraph 41.

These claim amendments and additions are made to clarify the subject matter therein; and these amendments are submitted in order to place the claims in condition for allowance, and do not disclaim any subject matter to which the Applicants are entitled.

Rejection Under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1 and 5 under 35 U.S.C. § 112, second paragraph, for being indefinite for allegedly not containing a positive process step which relates back to the preamble (Office Action mailed March 15, 2006, page 2). Applicants respectfully traverse this rejection.

Claim 1 has been modified to include a positive process step that relates directly back to the preamble. This modification also applies to claim 5 as claim 5 is dependent on claim 1 and thus, includes

all the limitations of claim 1. Specifically, claim 1 has been amended to clearly recite the step of simultaneously detecting signal intensities from the at least two markers.

It is thus submitted that the claims 1 and 5 meet the requirements of 35 USC § 112, second paragraph, and reconsideration and withdrawal of the present rejection is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

The Examiner rejected claims 1, 3, and 5 under 35 U.S.C. § 103(a) as unpatentable over Pillai, et al., (Cancer Epidemiology, Biomarkers and Prevention, 5:329-335, 1996) in view of U.S. Patent Application Serial No. US 2002/0045591 (Geiger, et al.) and U.S. Patent No. 6,756,207 (Giuliano, et al.) (Office Action mailed March 15, 2006, pages 2-6). Specifically, it is alleged that the claimed methods would have been *prima facie* obvious because there would have been motivation to combine the references and that the combined references somehow would teach each and every feature of the claims. Applicants respectfully traverse.

The Examiner also rejected claims 1 and 4 under 35 U.S.C. § 103(a) as unpatentable over Pillai, et al., (Cancer Epidemiology, Biomarkers and Prevention, 5:329-335, 1996) in view of U.S. Patent Application Serial No. US 2002/0045591 (Geiger, et al.) and U.S. Patent No. 6,756,207 (Giuliano, et al.) and further in view of Kihana, et al., (Cancer 73:148-153, 1994) (Office Action mailed March 15, 2006, pages 6-8). Applicants respectfully traverse.

The rejections are considered collectively.

As amended, the claims are drawn to methods for detecting tumor cells and their precursor cells in uterine cervical smears comprising contacting the cells with signaling reagents that specifically bind to at least two molecular markers of cervical cancer and simultaneously detecting color signal intensities from the markers. The claimed methods further comprise the step of combining the color signal intensities. The combined color signal intensities are then measured and accredited to achieve detection.

It is respectfully pointed out that "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *See In re Royka*, 490 F.2d 981, 180 (CCPA 1974) and M.P.E.P. § 2143.03. Further, "[i]f an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious." *See In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988). Here, it will be shown that none of the rejected claims are obvious over the asserted combinations of references as none of the references, either taken separately or together, teach or suggest each and every limitation of the claims.

Pillai, et al., relates to a study that investigates expression levels and interactions among p53, HPV-16/-18 E6 and bcl-2 and their relationship with the development of cervical cancer. More in particular, cervical smears having varying degrees of cervical disease were tested for the presence or

absence of p53, HPV-16/-18 E6, and bcl-2 using immunofluorescence microscopy. The smears were singularly stained with immunofluorescence-detectable antibodies against either p53, HPV-16/-18 or bcl-2 proteins. The immunofluorescence data was collected and analyzed by statistical methods to estimate cancer risks. Pillai, et al., does not contemplate at least two features of the presently claimed methods. First, Pillai, et al., does not at any point employ at least two molecular markers of cervical cancer that are simultaneously detected. Instead, Pillai, et al., separately stains samples with antibodies against the tested biomarkers, p53, HPV-16/-18 or bcl-2. No simultaneous detection is taught or suggested by Pillai, et al. Second, Pillai, et al., does not contemplate combining color signal intensities. Further, it does not contemplate measuring and accrediting the combined color signal intensities to achieve detection. Contrary to the claimed methods, Pillai, et al., separately measures and analyzes fluorescence intensities and never at any point contemplates combining fluorescence measurements. Rather, measurements are separately obtained, recorded and evaluated. At best, Pillai, et al., discloses only a manual method to estimate cancer risk through subjective consideration of separately obtained fluorescence data. This is a significant distinction in that the claimed methods, but not Pillai, et al., provide higher informative value of detection by combining, measuring and accrediting multiple marker intensities to make possible an objective detection of tumor cells or their precursors.

Considering Pillai, et al., in combination with Geiger, et al., or Giuliano, et al., it is apparent that neither Geiger, et al., nor Giuliano, et al., cure the aforementioned deficiencies of Pillai, et al. Geiger, et al., relates to methods and compositions for treating cancer with abnormally high levels of beta-catenin that include administering peptides with a beta-catenin binding domain. Giuliano, et al., relates to high content screening methods for measuring the effects of drugs on complex molecular events such as signal transduction pathways and on the temporal and spatial distribution of cellular materials in cell arrays. In contrast to the conclusions made in the Office Action, no where do Geiger, et al., or Giuliano, et al., either alone or in combination, contemplate the particular features of the claimed methods, including detection of two markers of cervical cancer simultaneously and combining their color signal intensities which are then measured and accredited to detect tumor cells and their precursors in a uterine cervical smear.

The Examiner states that Giuliano, et al., discloses fluorescence microscopy-based cell scanning methods that somehow teach or suggest the step of combining and accrediting the signal intensities of mixtures. The Examiner, in particular, points to exemplary assays of Giuliano, et al., relating to measuring the total or average fluorescent intensity within a cell or nucleus of marker colors and alleges that these assays teach or suggest the step of combining and accrediting according to the invention. It is believed that a further discussion of the methods in Giuliano, et al., will provide helpful clarification.

First, Giuliano, et al., does not even relate to cancer diagnosis but rather to the effects of candidate drugs on complex molecular events in a cell such as signal transduction pathways and on the

temporal and spatial distribution of cellular materials (*see, e.g.,* Col. 11, lines 11-19). To evaluate these changes, Giuliano, et al., relates to the use of automated cell scanning methods to detect fluorescence reporter molecules associated with intracellular structures (e.g., nucleus, cytoskeleton) and/or specific molecules (kinases) in the cell for the purpose of tracking the spatial and temporal location of the molecules in response to environmental conditions. For example, a main component of Giuliano, et al., relates to evaluating translocation of proteins in and out of the nucleus (*see, e.g.,* Example 1 at Col. 25). The methods employed by Giuliano, et al., involve staining the nucleus, using microscopy to define the cytoplasm, and then determining the difference in marker fluorescence of the stained translocation protein in the nucleus versus the cytoplasm. More in particular, "the average antibody fluorescence in each of these two regions [the nucleus versus cytoplasm] is determined, and the difference between these averages is defined as the NucCyt Difference" (See Col. 25, lines 66-67 to Col. 26, lines 1-2, emphasis added). Note that the fluorescence signals of the nucleus and the antibody-labeled translocation protein are not combined. This above aspect of Giuliano, et al., leads to a second distinction over the presently claimed methods.

In particular, Giuliano, et al., does not teach or contemplate, either expressly or impliedly, the steps of combining the color signal intensities of multiple markers and measuring and accrediting the combined color signal intensities. While Giuliano, et al., may relate to staining cells with multiple markers, for example, Hoechst DNA stain and a fluorescent antibody-stained transcription factor (See Example 1), the fluorescence measurements are measured separately and are never at any point combined in the way claimed by the present methods. Instead, Giuliano, et al.'s methods employ a first stain to define an area in the cell, such as the nuclear region, the cytoplasm, or the entire intracellular space. A second stain is used against a molecule of interest, such as a translocation protein, and comparative fluorescence data is obtained of it with respect to the spatial boundaries defined by the first stain. Example 1 can be referenced for clarity. There, the DNA is stained and imaged with the fluorophore Hoechst stain. The nucleus and cytoplasm space/boundaries are defined. Then, fluorescence data of an antibody-tagged transcription factor imaged both in and out of the nucleus is compared to understand the state of translocation of that protein.

In fact, Giuliano, et al.'s disclosed methods teach away from the presently claimed methods because the nature of the type of data obtained by Giuliano, et al., would not be feasible if the claimed steps of detecting color signal intensities and measuring and accrediting the combined color signal intensities were carried out. In other words, Giuliano, et al., teaches not to combine signal intensities and not to measure and accredit the combined signal intensities as its methods require the different fluorescent signals (e.g., nucleus and transcription factor) to be separately considered and analyzed. Relevant case law holds that "If the proposed modification or combination of the prior art would change the principle of

operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." *In re Ratti*, 270 F.2d 810 (CCPA 1959). Here, the principle of operation of Giuliano, et al., would necessarily be changed if operated in accordance with the claimed methods. As such, Giuliano, et al., is not a proper reference under Section 103. Also, for the same reasons, there would be no reasonable expectation of success of carrying out the present invention with Giuliano, et al., in hand since Giuliano, et al., teaches away from the claimed methods and because its principle of operation would be changed. Since a *prima facie* case of obviousness requires a reasonable expectation of success, Giuliano, et al., either alone or in combination with Pillai, et al., cannot render the invention *prima facie* obvious. See M.P.E.P. 2143.02.

Third, Giuliano, et al., requires substantial subjective analysis in its methods, for example, "interpreting the digital image data to determine the distribution, environment or activity of the fluorescently-labeled reporter molecules in the individual cells (i.e., intracellular measurements) and the distribution of the cells to test for specific biological functions" (See Col. 21, lines 23-27). It is taught that as a final phase of its scanning methods, fluorescence data, cell images, statistical analysis reports, graphical reports of data, should all be examined by the user of the method (*see, e.g.*, Col. 20, lines 17-49). Thus, one skilled in the art would understand that Giuliano, et al., requires substantial subjective analysis of its generated data. Given this distinction, Giuliano, et al., certainly does not contemplate automatically combining, measuring and accrediting color signal intensities to achieve detection of a disease state (e.g., cervical cancer).

Accordingly, Giuliano, et al., for the reasons outlined above, does not cure the aforementioned deficiencies of Pillai, et al., and thus, does not either alone or in combination teach or suggest the claimed invention. Similarly, Geiger, et al., for the aforementioned reasons cannot be combined with Pillai, et al., to arrive at the claimed methods.

Taking the cited references in further combination with Kihana, et al., it is apparent that the combination still falls short of the claimed methods. Kihana, et al., relates to a study that examines the role of her2/neu in cervical cancer by immunohistochemically analyzing cervical adenocarcinoma tissue sections for the expression of her2/neu. However, Kihana, et al., does not teach or suggest any of the features of the presently claimed methods, for example, detection of at least two markers of cervical cancer simultaneously and accrediting color signal intensities obtained from the simultaneous detection of the markers. As such, Kihana, et al., does not cure the deficiencies of the cited references and cannot be combined with any other cited references to arrive at the claimed methods.

Even if the combination of cited references would teach or suggest the elements of the claimed methods (and they do not) it is respectfully submitted that the selection of references is based on improper

hindsight reasoning. Simply picking and choosing the elements of the claimed invention from among many different options in the art is hindsight and does not satisfy the requirements of 35 U.S.C. § 103.

Accordingly, as Pillai, et al., Geiger, et al., Giuliano, et al., and Kihana, et al., either taken alone or in combination with each other, fail to teach or suggest each and every element of the invention as presently presented and thus, cannot render the present claims *prima facie* obvious. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 are respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants submit that the claims are in condition for allowance and Applicants respectfully request reexamination of the present application, reconsideration and withdrawal of the present rejections and objections, and entry of the amendments. Should there be any further matter requiring consideration, Examiner Ungar is invited to contact the undersigned counsel.

If there are any further fees due in connection with the filing of the present reply, please charge the fees to undersigned's Deposit Account No. 13-3372. If a fee is required for an extension of time not accounted for, such an extension is requested and the fee should also be charged to undersigned's deposit account.

Respectfully submitted,

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